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Abstract Text:

Introduction: Nontuberculous mycobacteria (NTM) are environmental microbes, capable of colonizing and infecting humans following inhalation of the bacteria. Both incidence and prevalence of this disease have been increasing, with estimates as high as a 2-5-fold increase for some populations (1). Though exposure to mycobacteria in the environment is common, most healthy individuals do not develop infections. Instead, infections develop in vulnerable populations with pre-existing conditions such as Cystic Fibrosis or Chronic Obstructive Pulmonary Disease (COPD).

Mycobacterium avium complex (MAC) are NTM common in infections and known to form biofilms in the environment. Studies have shown these biofilms to have apoptotic effects on immune cells *in vitro*. NTM biofilms have been observed in lungs of COPD patients (2). However, the role and dynamics of biofilms *in vivo* remains unclear.

Materials and Methods: In this work, we take a computational approach to explore the initial dynamics of biofilm-forming mycobacteria and the associated innate immune response in patient lungs. We use a spatio-temporal agent-based computational model to simulate the dynamics of host innate immune defenses (macrophage phagocytosis, recruitment, apoptosis and antibacterial properties), as well as bacterial events (growth, replication, biofilm formation and induction of macrophage apoptosis). The model tracks fates of individual cells, as well as quantifying the effect of cellular scale events on tissue scale infection dynamics.

Model parameters are estimated based on host-pathogen interactions and environmental measurements obtained from *in vitro* studies as well as *in vivo* from healthy and diseased patients. Parameters not available in literature are estimated based on model calibration to in vivo measurements. Sensitivity analysis is performed by simultaneously varying model parameters and calculating partial rank correlation coefficients between model parameters and outputs of interest.
Results and Discussion: To isolate the effect of biofilm on host-pathogen interactions, we perform a focused sensitivity analysis on parameters that directly affect biofilm formation and macrophage phagocytosis. This sensitivity analysis revealed both time for the bacterial population to reach exponential growth and the percentage of infections sterilized are positively correlated with the bacterial ability to switch phenotype between growing or producing biofilm. High bacterial proliferation rates yielded low percentage of infections sterilized and the bacterial population quickly moving into exponential growth. Slower growth rates and increased biofilm production yielded the highest sterilization percentages, and significantly slower movement toward exponential growth. This indicates that even with bacteria more quickly producing biofilm, they were still at high risk for phagocytosis, in which the bacterium were either killed or managed to infect the macrophage, delaying their exponential growth. These observations indicate a need for more detailed representation of bacterial phenotype switching between planktonic and sessile phenotypes, and how they affect population growth.

The model also reveals sensitivity to macrophage probability of killing a bacterium it has phagocytosed (rather than becoming infected). In simulations with high probability of killing, a bimodal outcome was observed in which the first 48 hours determined whether macrophages either cleared the infection or bacteria reached exponential growth. This was shown by both high percentage sterilized and low time-to-exponential growth measurement representing both best-case scenario (sterilization) or “worst” infections that would lead to acute disease. Meanwhile, macrophages with lower probabilities of killing more often became infected, thus delaying the

growth of bacterial populations and recruiting more macrophages for a granuloma-like structure, but failing to sterilize infections.

Conclusions: Our model quantifies the relative contributions of important biological factors of MAC infections in the lungs, including the role of biofilm and its effects on host-pathogen interactions. Further iterations of this model will include antibiotic regimens to provide a basis for optimizing treatment of these infections.

References:

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